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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,789	MELTON ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,14,16-19,50-52,55,56 and 64-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,14,16-19,50-52,55,56 and 64-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/23/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 11/23/2010, are acknowledged and entered. Claims 2, 12-13, 15, 20-49, 53-54, and 57-63 have been cancelled by Applicant. Claims 64-70 are newly presented. Claims 1, 3-11, 14, 16-19, 50-52, 55-56, and 64-70 are pending and under examination.

Election/Restrictions

In light of the amendments to claims 50-52 and 55-56 are no longer considered withdrawn from consideration as being directed to a non-elected invention because the amended claims encompass the same administration step(s) and patient population recited in claim 1.

Response to Arguments

Any previous rejections and/or objections to claims 2, 12-13, 15, 20-49, 53-54, and 57-63 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 11/23/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 11/23/2010 was filed after the mailing date of the Non-Final Office Action on 6/30/2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 7 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the limitation, "plasma level indicating toxicity at a given time after administration", as recited in claim 5 are not clear.

Response to Arguments

Applicants argue that this rejection is obviated by the amendment to claim 5, reciting that the level is a plasma level which indicates toxicity and such a plasma level is exemplified in the specification at page 17, lines 25-29.

Applicants' arguments are not persuasive because limitations from the specification are not imported into the claims. The Examiner suggests amending claim 5 to recite the plasma levels disclosed in the specification at page 17, lines 25-29.

Claim Rejections - 35 USC § 112 – 1st Paragraph, New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first

paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. This is a New Matter rejection.

Claim 9 has been amended such that it is limited to one or more clinical symptoms of toxicity specifically caused by raltitrexed. Such toxicities are disclosed in the specification at page 18, lines 27-29. This list does not include anorexia as recited in the Markush group in claim 9.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-10, 19, 50-52, 55-56, 64-67, and 69-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Adamson et al.** (J. Clin. Oncol., 1991, vol. 9, pages 670-674), **Adamson et al.** (J. Clin. Oncol., 1992, vol. 10, pages 1359-1364), **DeAngelis et al.** (J. Clin. Oncol., 1996, vol. 14, pages 2145-2149), and **Krause et al.** (Leukemia and Lymphoma, 2002, vol. 43, no. 11, pages 2139-2143) in view of **Clarke et al.** (Clin. Pharmacokinetics, 2000, vol. 39, no. 5, pages 429-443), **Kalghatgi et al.** (Enzymes and Drugs, J. Holcenberg and J. Roberts,

eds., Wiley, New York, 1981, pages 77-102), and **Bisset et al**. (J. Med. Chem., 1992, vol. 35, pages 859-866) (newly cited).

Claimed Invention

The instant claims recite methods of combating toxicity caused by raltitrexed, comprising administering to the individual carboxypeptidase G2 (EC 3.4.22.12).

Teachings of Adamson et al. (1991)

Adamson et al. teach that the carboxypeptidase G class of enzymes rapidly hydrolyze methotrexate (MTX) into the inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA) and glutamate (Abstract). The instant study of Adamson et al. evaluated the use of carboxypeptidase G_2 ($CPDG_2$) as a potential intrathecal rescue agent for massive MTX overdose (id.).

Groups of monkeys received (1) MTX alone (5 mg), (2) MTX (5 mg) followed 5 minutes later by $CPDG_2$ (30 U), or (3) $CPDG_2$ (30 U) alone (page 671, left column, "Pharmacokinetics of $CPDG_2$ Rescue"). As shown in Figure 1, administration of $CPDG_2$ resulted in a greater than 400-fold decrease in MTX concentrations (page 671, right column).

Carboxypeptidase G enzymes such as $CPDG_1$ and **$CPDG_2$** have been administered systemically to patients as rescue therapy following high-dose MTX and also have been used to detoxify patients with renal failure following MTX dosing (page 672, right column).

The authors conclude that $CPDG_2$ may prove to be an important addition to the currently recommended strategy for the management of MTX overdose (page 673, right column).

Teachings of Adamson et al. (1992)

Similar to Adamson et al. (1991), Adamson et al. (1992) teaches that $CPDG_2$ rapidly hydrolyzes MTX to inactive metabolites and has more potential advantages than standard leucovorin rescue (Abstract). The authors studied the effects of $CPDG_2$ administration to monkeys administered 300 mg/m^2 MTX loading dose followed by a 60 mg/m^2/hour infusion of MTX during an 18 hour period (id.). 0.5 mL $CPDG_2$ (50 U/kg) was administered by IV on

completion of the MTX infusion (page 1360, right column). As shown in Figure 2, $CPDG_2$ dramatically decreased plasma MTX concentrations to "nontoxic levels" (Abstract; Figure 2).

Teachings of DeAngelis et al.

DeAngelis et al. studied the safety and efficacy of carboxypeptidase G_2 (CPG_2) rescue for high-dose MTX in patients with recurrent cerebral lymphoma (Abstract). Four patients with recurrent primary CNS lymphoma received 3.0 mg/m^2 MTX infused over 2 hours and twelve hours after the start of MTX, 50 U/kg CPG_2 was infused and a second dose of CPG_2 was given 6 hours after the first (Abstract; pages 2145-2146, "Patients and Methods"). All patients had a rapid and prominent decrease in plasma MTX concentration within 5 minutes of CPG_2 administration (paragraph bridging pages 2146 and 2147; Figure 1). The authors conclude that, unlike leucovorin, CPG_2 rescues organs by terminating their exposure to MTX (paragraph bridging pages 2147 and 2148). The treated patients had no evidence of MTX toxicity with CPG_2 rescue (page 2148, left column).

Teachings of Krause et al.

Krause et al. teach that high-dose methotrexate (MTX) is a component of many cancer treatment regimens but that, despite careful management, delayed renal clearance followed by extremely high serum levels with potentially life-threatening toxicity can occur. In the present study, the authors evaluated carboxypeptidase G_2 ($CPDG_2$) rescue in 8 patients with delayed methotrexate elimination and renal impairment after high-dose MTX therapy for lymphoma and osteosarcoma (Abstract).

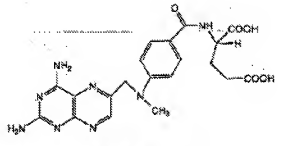
Patients were treated with six cycles of chemotherapy containing combinations of methotrexate (5 g/m^2 over 24 hours) and other chemotherapeutic agents. Carboxypeptidase G_2 was administered in a dose of 50 U/kg over 5 minutes (page 2140, right column). As shown in Figure 1, $CPDG_2$ administration dramatically lowered MTX plasma concentration in the treated patients.

The authors conclude that $CPDG_2$ is highly effective in preventing life-threatening toxicity in patients with MTX induced renal failure and delayed drug clearance and is safe and well tolerated (page 2143, left column).

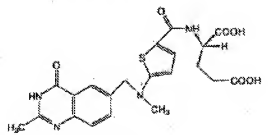
Teachings of Clarke et al.

Clarke et al. teach that raltitrexed is a specific, folate-based inhibitor of thymidylate synthase with activity in advanced colorectal cancer (page 429). Apart from polyglutamation, raltitrexed does not appear to be metabolized to a significant extent and most of the excreted drug is recovered unchanged in the urine within the first 24 hours post-administration (page 430). While the average clearance of raltitrexed in 2.4 L/h (40 mL/min.), this value is significantly reduced in patients with compromised renal function and these patients are more likely to experience severe antiproliferative toxicity with raltitrexed (id.). In this regard, a study in cancer patients with renal impairment administered 3 mg/m2 raltitrexed every 3 weeks demonstrated that while there were no significant differences in mean C_{max} between patients with renal impairment and those without, the mean AUC was significantly higher in patients with renal impairment and treatment-related toxicities were significantly greater in patients with renal impairment (pages 437-438).

Figure 1 of Clarke et al. shows the structural similarity of ralititrexed to methotrexate.



Methotrexate

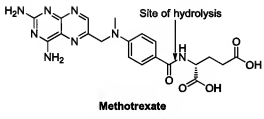


Raltitrexed

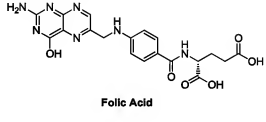
Teachings of Kalghatgi et al.

Kalghatgi et al. carboxypeptidase G enzymes hydrolyze the peptide bond of folate antagonists (page 82; page 83, Figure 3). Regarding substrate specificity of carboxypeptidase G enzymes, the authors teach that the enzymes from different sources exhibit considerable variation in substrate specificity, however all carboxypeptidase G enzymes hydrolyze folate derivatives with glutamic acid at the C-terminal (page 86).

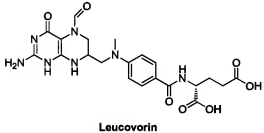
Table 2 demonstrates that carboxypeptidase G enzymes hydrolyze the C-terminal glutamate from methotrexate, 4-amino,^{10}N-methylpteroylaspartic acid, aminopterin, 4-aminopteroylaspartic acid, folic acid, leucovorin, and 5-methyltetrahydrofolic acid.



Methotrexate



Folic Acid



Leucovorin

Teachings of Bisset et al.

Bisset et al. is provided as evidence that raltitrexed is a substrate for carboxypeptidase G_2. In this regard, the authors demonstrate that raltitrexed is hydrolyzed by carboxypeptidase G_2 in the same position as methotrexate (Scheme II; page 863, left column). In Scheme II of Bisett et al., compound **8** is raltitrexed, a compound of the instantly claimed Formula I when R^1 is OH, R^2 is methyl, B is Formula Ia (wherein A^1 and A^2 are CH and R^{5a} is hydrogen), X is $-CH_2NR^{7b}$ (wherein R^{7b} is methyl), A^6 is S, R^8 is hydrogen, R^3 is hydrogen, and R^4 is $-CH_2C(R^{9a})(R^{9b})$-D (wherein R^{9a} and R^{9b} are H and D is C(O)OH).

Examiner's Determination of Obviousness

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer carboxypeptidase G_2 to combat toxicity associated with the administration of raltitrexed. The skilled artisan would have been motivated to do so because carboxypeptidase G_2 was known in the art to effective in reducing the toxicity of the related antifolate compound, methotrexate, via hydrolyses of the C-terminal glutamate of methotrexate. As evidenced by Bisset et al., raltitrexed is also a substrate for carboxypeptidase G_2, wherein the C-terminal glutamate of raltitrexed is also hydrolyzed by the enzyme. As such, the skilled artisan would expect that administration of carboxypeptidase G_2 to patients undergoing treatment with raltitrexed would result in lowering of raltitrexed plasma concentrations and reduction in toxicity, just as is seen in patients administered carboxypeptidase G_2 who are undergoing treatment with methotrexate.

Applicants predicate patentably of their invention in part on the fact that raltitrexed is a substrate for carboxypeptidase G_2. Applicants state that it was not known whether any folate compounds other than folic acid, MTX, 5-methyl THF, and 5-formyl THF were substrates for CPG_2 and it was not known, and could not be predicted, whether any of the new generation of antifolate drugs are substrates for CPG_2 cleavage (page 7, lines 12-15). However, as evidenced by Bisset et al., this is not the case. It was known prior to Applicants' invention that raltitrexed was a substrate for CPG_2 and is hydrolyzed by CPG_2. As such, Applicants' demonstration that CPG_2 cleaves raltitrexed is not a patentable contribution to the art.

Response to Arguments

Firstly, Applicants argue that each of Adamson I, Adamson II, DeAngelis, and Krause relates to the use of carboxypeptidase G2 for treating methotrexate toxicity and there is nothing in these references to teach or suggests that carboxypeptidase G2 may be useful for treating toxicity caused by ralititrexed.

Secondly, Applicants argue that Kalghatgi is a general review of folate-degrading enzymes with special emphasis on carboxypeptidase G. Applicants argue that the structure of raltitrexed is "quite different" from the antifolates studied by Kalghatgi in so far as while raltitrexed has a C-terminal glutamate residue the immediately adjacent benzene ring is replaced

by the heteroaromatic moiety thiophene. Applicants assert that the ordinary skilled artisan would not understand thiophene to be an isosteric replacement for benzene.

Thirdly, Applicants argue that Springer et al. (1995), which Applicants submitted in the IDS filed 1/4/2007 suggest that modifications to the benzene ring of methotrexate may actually be detrimental to carboxypeptidase activity. As such, Applicants argue that the ordinary skilled artisan would not be able to predict whether raltitrexed would be hydrolyzed by carboxypeptidase G2 at sufficient rate to combat toxicity.

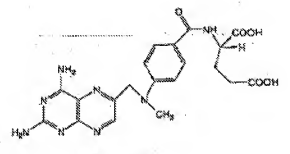
Fourthly, Applicants argue that Clarke merely discloses that clearance of raltitrexed is significantly reduced in patients with compromised renal function, making these patients more likely to experience severe antiproliferative toxicity. Applicants argue that there is nothing in Clarke et al. to teach or suggest a solution to this problem.

Fifthly, Applicants argue that Bisset teaches that carboxypeptidase G2 can be used in a synthetic chemical process to prepare poly-g-glutamyl conjugates of raltitrexed and other quinazoline antifolates but does not disclose that administration of carboxypeptidase G2 can be used to combat the toxicity of raltitrexed in an individual nor any suggestion of such administration. It is important to note that Applicants admit that Bisset shows that carboxypeptidase G2 can cleave raltitrexed for synthetic chemical purposes, which admission will be discussed in further detail below.

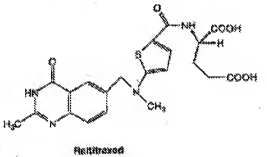
Applicants' arguments have been carefully considered but they are not persuasive. As a first matter, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Applicants attack the individual teachings of the cited prior art, but fail to establish that the skilled artisan would not have been motivated to try carboxypeptidase G2 for combating toxicity associated with raltitrexed administration based on the combined teachings of the cited prior art as discussed supra.

With regard to Applicants' argument that the structure of raltitrexed is "quite different" than that of other anti-folates such as methotrexate, this argument is not persuasive. The

structures of raltitrexed and methotrexate are quite similar and both have the same mechanism of action.



Methotrexate



Raltitrexed

Contrary to Applicants' assertion, thiophene and benzene are well known isosteres as evidenced by Patani et al. (Chem. Rev., 1996, vol. 96, pages 3147-3176). This reference is cited only in response to Applicants' assertion that the skilled artisan would not understand thiophene to be an isosteric replacement for benzene. At page 3158, left column, under the heading "Ring Equivalents", Patani et al. state unequivocally that, "[T]he use of the **classical bioisosteres** benzene, thiophene, and pyridine resulted in analogues with retention of biological activity within different series of pharmacological agents" (emphasis added). Given their related structures, similar mechanisms of action, and similar toxicities, the skilled artisan would expect that an enzyme that cleaves methotrexate would also cleave raltitrexed and thus be useful in combating raltitrexed toxicity.

In this regard, it was known in the art that carboxypeptidase G2 can cleave raltitrexed for synthetic chemical purposes. Thus, despite Applicants' arguments that raltitrexed has a structure "quite different" from other anti-folates and was not known to be a substrate of carboxypeptidase G2, Bisset et al. teach that raltitrexed is a substrate for carboxypeptidase G2. Applicants attempt

to gloss over this fact by arguing that Bisset teaches that carboxypeptidase G2 can be used in a synthetic chemical process to prepare poly-γ-glutamyl conjugates of raltitrexed and other quinazoline antifolates but does not disclose that administration of carboxypeptidase G2 can be used to combat the toxicity of raltitrexed in an individual nor any suggestion of such administration. Applicants further argue that the affinity of the enzyme for a substrate can vary enormously and is a critical feature for combating toxicity. Applicants argue that in a synthetic context such as found in Bisset a relatively low affinity could result in a useful reaction mechanism. However, Applicants argue, in therapeutic terms the reaction could still effectively cease at substrate concentrations that would be toxic in an individual. Applicants argue that it was their work that established the kinetics of the reaction between carboxypeptidase G2 and raltitrexed. Their results show that the enzyme had high affinity for raltitrexed (7.8 μM), comparable with that for methotrexate (8 μM). It is the Examiner's position that this is precisely what the skilled artisan would expect given the fact that methotrexate and raltitrexed have similar structures and mechanisms of action and are both cleaved by carboxypeptidase G2. Further, in view of the fact that carboxypeptidase G2 was known to be effective in combating methotrexate G2 in human subjects, the skilled artisan would have been motivated to try carboxypeptidase G2 for combating raltitrexed toxicity.

Applicants conclude by arguing that more than a decade passed after the Bisset publication and Applicants' own filing and yet no one had contemplated the use of carboxypeptidase G2 to cleave raltitrexed to reduce its known toxicity. Applicants argue that this is a very clear long felt need, a well recognized secondary consideration indicating the non-obviousness of the present invention. Applicants are directed to MPEP 716.04 for a discussion of the criteria needed to meet the requirement of satisfying a long-felt need. It is the Examiner's position that while reducing the toxicity of raltitrexed meets the requirement for a long-felt need, i.e., the art recognizes that raltitrexed administration leads to toxicity, Applicants have not established that there were prior unsuccessful attempts to combat raltitrexed toxicity. Further, the failure to solve a long-felt need may be due to factors such as lack of interest or lack of appreciation of an invention's potential or marketability rather than want of technical know-how.

Scully Signal Co. v. Electronics Corp. of America, 570 F.2d 355, 196 USPQ 657 (1st. Cir. 1977) (emphasis added).

In the instant case, carboxypeptidase G2 was known to be useful in combating toxicity associated with the administration of the anti-folate methotrexate. Raltitrexed has a similar structure and mechanism of action as methotrexate, was known to have similar toxicity, and was known to be a substrate for carboxypeptidase G2. As such, it would have been obvious to one of ordinary skill in the art to try carboxypeptidase G2 for combating toxicity associated with raltitrexed administration with a reasonable expectation of success.

The Examiner acknowledges that any finding of obviousness requires that there be a reasonable expectation of success. MPEP 2143.02(1). Moreover, absolute predictability is not required for obviousness, but at least some degree of predictability is required for there to be a reasonable expectation of success. See MPEP 2143.02 (1). Further, the Examiner acknowledges that the individual references do not explicitly teach the combination of raltitrexed and carboxypeptidase G2. However, Applicants are reminded that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Claims 11, 14, 16-18 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Adamson et al**. (J. Clin. Oncol., 1991, vol. 9, pages 670-674), **Adamson et al**. (J. Clin. Oncol., 1992, vol. 10, pages 1359-1364), **DeAngelis et al**. (J. Clin. Oncol., 1996, vol. 14, pages 2145-2149), and **Krause et al**. (Leukemia and Lymphoma, 2002, vol. 43, no. 11, pages 2139-2143) in view of **Clarke et al**. (Clin. Pharmacokinetics, 2000, vol. 39, no. 5, pages 429-443), **Kalghatgi et al**. (Enzymes and Drugs, J. Holcenberg and J. Roberts, eds., Wiley, New York, 1981, pages 77-102), and **Bisset et al**. (J. Med. Chem., 1992, vol. 35, pages 859-866) (newly

cited) as applied to claims 1-10, 19, 25-36, 40-46, and 62-63 above, and further in view of **Widemann et al**. (J. Clin. Oncol., 1997, vol. 15, no. 5, pages 2125-2134) (newly cited) (Abstract attached).

Adamson et al. (1991), Adamson et al. (1992), DeAngelis et al., Krause et al., Clarke et al., Kalghatgi et al., and Bisset et al. teach as applied supra and are herein applied in their entirety for the same teachings. Claims 10-18 and 37-39 differ from Adamson et al. (1991), Adamson et al. (1992), DeAngelis et al., Krause et al., Clarke et al., Kalghatgi et al., and Bisset et al. in that the references do not teach a folate pathway rescue agent such as leucovorin.

Teachings of Widemann et al.

Widemann et al. teach that $CPDG_2$ rapidly hydrolyzes methotrexate to inactive metabolites. Widemann et al. teach administration of one to three doses $CPDG_2$ (50 U/kg), thymidine (8 g/m2), and leucovorin to patients with high-dose methotrexate-induced renal dysfunction (Abstract).

Examiner's Determination of Obviousness

It would have been prima facie obvious to administer carboxypeptidase G_2 in combination with leucovorin to reduce toxicity associated with administration of raltitrexed for the reasons discussed supra, in view of the teachings of Widemann et al., who teach co-administration of $CPDG_2$ and leucovorin rescues patients with high-dose MTX nephrotoxicity. As such, the skilled artisan would expect that $CPDG_2$ and leucovorin would also be effective to reduce toxicities associated with raltitrexed therapy given the fact that raltitrexed was known to also be a substrate of $CPDG_2$ as taught in Bisset et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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